IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Alma R. Smalling

Applicant	: Wenlong Deng	Confirmation No. 1639
Application No.	: 10/510,617	
Filed	: October 7, 2004	
Title	: A PHARMACEUTICAL COMPOSITION FOR TREATING RHEUMATISM AND THE PREPARATION THEREOF	
Grp./Div.	: 1655	
Examiner	: Patricia A. Leith	
Docket No.	: 53624/C306	

PETITION UNDER 37 CFR 1.182 AND/OR 1.183 TO FILE A SUBSTITUTE TRANSLATION OF THE PCT SPECIFICATION

Mail Stop PCT
Attention: PCT Legal
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 7068
Pasadena, CA 91109-7068
July 29, 2009

Commissioner:

In response to the Office action dated April 29, 2009, Applicant hereby petitions the Commissioner to enter a substitute, English translation of the PCT specification in the above-identified US national stage application. A certified substitute specification is attached, and the requisite petition fee is enclosed. A one-month extension of time petition is also being filed concurrently herewith.

Applicant seeks "*nunc pro tunc*" entry of the substitute specification in the form provided herewith, and re-entry of the new title and "Cross-Reference to Related Application" as filed in the Preliminary Amendment dated October 7, 2004.

Statement of Facts

This application is a U.S. national stage patent application and claims priority of international application number PCT/CN2002/00246 filed on April 9, 2002. When the national stage application was filed, a copy of the international application (in Chinese) was provided, and Applicant submitted a certified English translation of the application. Unfortunately, the quality of that translation has subsequently been determined to be quite low, and this has been reflected in repeated objections by the Examiner during prosecution of the national stage application.

On multiple occasions, Applicant attempted to amend the specification to improve its clarity, grammar, syntax, and idiomatic expressions. Unfortunately, this resulted in further objections by the Examiner on the ground that the amendments purportedly introduced "new matter" into the application. Applicant does not believe that any such new matter was entered, but Applicant does wish to comply with all rules and regulations.

In the April 29, 2009 Office action, the Examiner indicated that the application is in condition for allowance except for the specification, which was again characterized as containing new matter. Summarizing a prior telephone conversation with the undersigned, the Examiner wrote:

> [T]he Examiner suggested that the Applicant expressly abandon this case and file a CIP with a new specification in order to remedy the specification under objection. Alternatively, the Examiner indicated that an Ex parte Quayle action could be instituted in order to permit Applicant time to file a substitute translated specification of the PCT specification. A phone call to PCT Legal by the Examiner revealed that a new translation of the original PCT document would only be entertained via Petition to PCT Legal.

April 29, 2009 Office action, page 3.

Applicant submits that it should not be required to file a CIP application. Instead, Applicant should be permitted to replace the original certified translation, *nunc pro tunc,* with a high quality substitute translation. Applicant has obtained such a translation from a reputable translation company. A copy of the new translation is attached as Exhibit A. A notarized

certification that the "English translation conforms essentially to the original Chinese language" is attached as Exhibit B. This certification is tantamount to a statement that the substitute specification does not contain new matter.

Points to be Reviewed

The sole question before the Commissioner is whether Applicant should be permitted to replace the original English translation of the Chinese language PCT application with a new English translation that is certified to conform to the original Chinese -- i.e. a translation that does not contain new matter. Applicant submits that the Office has the authority under 37 C.F.R. 1.182 and/or 1.183 to grant this petition, and that the requested relief is appropriate. In particular, Applicant first notes that the Examiner has invited Applicant to proceed by way of petition (as Applicant does not wish to file a CIP application). See, Office action dated April 29, 2009, at pages 3-4. Applicant also notes that it has previously complied with all statutes and regulations pertaining to the entry into the national stage, including a submission of a certified English translation of the Chinese language PCT application. Unfortunately, the original translation has proven to be of poor quality. As Applicant has now obtained a certified substitute translation of the specification, the Office should enter the specification into the file, *nunc pro tunc*, in place of the previously submitted specification.

Requested Relief

1. Applicant seeks *nunc pro tunc* entry of the substitute translated specification as the official specification for this application.

2. Applicant seeks to preserve the amendment to the title and the introduction of a "Cross-Reference to Related Application" provided in the preliminary amendment filed October 7, 2004.

Applicant has identified the factual and procedural grounds for granting this petition, has included the certified substitute specification that it wishes to have entered, and has indicated the relief that it seeks. In addition, Applicant has filed herewith the requisite fee under 37 C.F.R. 1.17(f). Accordingly, Applicant respectfully requests that the Office grant this petition. If the Office determines that the requested relief can only be granted by suspending the rules,

Applicant hereby petitions, under 37 C.F.R. 1.183, to suspend the rules and grant the requested relief on the same grounds presented above.

The Office is hereby authorized to charge any fees that this paper may require under 37 C.F.R. 1.16 and 1.17 to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account.

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By _____
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Reg. No. 34,133
626/795-9900

JDC/jr
Enclosures

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ANTI-RHEUMATISM MEDICATION AND ITS METHOD OF PREPARATION

Field of technology

The present invention involves a medication and its method of preparation; in particular it involves a traditional anti-rheumatism Chinese medication and its method of preparation.

Background of the technology

Rheumatism and rheumatoid arthritis (RA) are generally considered to be difficult-to-treat diseases. Approximately 18 million RA patients are disabled by the disease. Research into new medications to treat RA has already been underway for almost a century. Aspirin was the earliest medication widely used for RA. Medications to treat RA may be generally divided into two types: non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressants. NSAIDs include diclofenac and other anti-inflammatories and adrenal cortical hormones. Clinical studies demonstrate that NSAIDs are effective. Immunosuppressants and cytotoxic medications include methotrexate, cyclophosphamide, and penicillamine, among others. In recent years, immunomodulation has been used as a method for treating rheumatic diseases. All anti-rheumatism drugs have been shown to have serious side effects and to date, a high-efficacy, low-toxicity medication has not yet been developed.

There are three main areas of emphasis in the research and development of anti-rheumatism drugs. The first includes NSAIDs and cytokine antagonists, such as recombinant soluble tumor necrosis factor antagonists, interleukin-1 receptor antagonists and platelet activation factor inhibitors. The second area is new immunosuppressants or immunomodulators, such as cyclosporin A. The third area is compound medications.

Early treatment of *bi* syndrome (obstruction of qi and blood, RA) in the field of traditional Chinese medicine can be dated to the ancient Chinese physician Zhang Zhongjing, "decoction of herba ephedrae, semen armeniacae amarum, gypsum fibrosum and radix glycyrrhizae," "decoction of radix stephaniae tetrandrae and radix astragali" and "decoction of radix aconite." *Kniphofia uvaria* is a plant that grows wild in Sichuan Province, and in local area clinical trials (in Sichuan) it has been proven to have definite therapeutic efficacy for patients with rheumatism. Unfortunately, at the same time many uncontrollable problems and serious side effects on the human reproduction system have been observed.

In traditional Chinese medicine, there is a long history of treating *bi* syndrome, and in past eras, physicians have developed traditional Chinese medications to treat it. There are a number of medications with high therapeutic efficacy. In the 1995 and 2000 editions of the Chinese Pharmacopeia are collected

no fewer than 80 single medications and 29 proprietary medications to treat *bi* syndrome. But there are problems, chiefly ① therapeutic efficacy against severe *bi* syndrome such as rheumatoid arthritis is still less than ideal, ② the preparation's dosage form cannot meet the needs of today's lifestyle, ③ a small number of medications possess therapeutic efficacy that could be termed good yet with major toxic side effects, such as the *Radix tripterygii wilfordii* preparation. This necessitates research and development of an anti-rheumatism medication with high efficacy and low toxicity, in a dosage form suited to today's lifestyle and medication-use habits, in particular a medication with treatment efficacy that can approach the efficacy of synthetic anti-rheumatism medications and has relatively mild side effects.

Contents of the technology

The objective of the present invention is to provide a compound medication with anti-rheumatism effect, high efficacy and low toxicity, and convenient administration. A further objective of the present invention is to provide a method for preparing the medication with anti-rheumatism effect.

The technical proposal for the medication of the present invention optimally is realized through the following materials:

Tripterygium hypoglaucum (Level) Hutch

Epimedium brevicornum Maximowicz

Lycium barbarum L.

Cuscuta chinensis Lamarck

Cuscuta australis R. Br.

The medication of the present invention is prepared from the above materials.

The materials may be composed of *Tripterygium hypoglaucum (Level) Hutch* together with any one or two or three of the other medications above.

The optimal materials formula proportions for the present invention are:

1-4 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

1-4 parts *Epimedium brevicornum Maximowicz* by weight

1-4 parts *Lycium barbarum L.* by weight

1-4 parts *Cuscuta chinensis Lamarck* by weight

Further, the optimal materials formula proportions for the present invention are:

2 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

2 parts *Epimedium brevicornum Maximowicz* by weight

1 parts *Lycium barbarum L.* by weight

1 parts *Cuscuta chinensis Lamarck* by weight

Further, the preferred materials formula proportions for the present invention are:

1-4 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

1-4 parts *Epimedium brevicornum Maximowicz* by weight

Further, the preferred materials formula proportions for the present invention are:

2 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

2 parts *Epimedium brevicornum Maximowicz* by weight

Further, the preferred materials formula proportions for the present invention are:

1-4 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

1-4 parts *Epimedium brevicornum Maximowicz* by weight

1-4 parts *Lycium barbarum L.* by weight

Further, the preferred materials formula proportions for the present invention are:

2 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

2 parts *Epimedium brevicornum Maximowicz* by weight

1 part *Lycium barbarum L.* by weight

Further, the preferred materials formula proportions for the present invention are:

1-4 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

1-4 parts *Epimedium brevicornum Maximowicz* by weight

1-4 parts *Cuscuta chinensis Lamarck* by weight

Further, the preferred materials formula proportions for the present invention are:

2 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

2 parts *Epimedium brevicornum Maximowicz* by weight

1 part *Cuscuta chinensis Lamarck* by weight

The amount of the glucoside $C_{33}H_{40}O_{15}$ from *Epimedium brevicornum Maximowicz* in the materials compound above should be no less than 2.0 mg.

Further, the preferred materials formula proportions for the present invention are:

1-4 parts *Tripterygium hypoglaucum (Level) Hutch* by weight and 1-4 parts *Lycium barbarum L.* by weight and/or 1-4 parts *Cuscuta chinensis Lamarck* by weight

Further, the preferred materials formula proportions for the present invention are:

2 parts *Tripterygium hypoglaucum (Level) Hutch* by weight and 1 part *Lycium barbarum L.* by weight and/or 1 part *Cuscuta chinensis Lamarck* by weight

With the above materials proportions by weight, routine preparation technology may be used to prepare any clinically acceptable medication form, such as pill, dispersant, cream, tablet, capsule (hard capsule or soft capsule), granule, injection, etc.

The method for preparing the medication of the present invention is:

Materials by weight:

1-4 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

1-4 parts *Epimedium brevicornum Maximowicz* by weight

1-4 parts *Lycium barbarum L.* by weight

1-4 parts *Cuscuta chinensis Lamarck* by weight

After *Tripterygium hypoglaucum (Level) Hutch* and *Epimedium brevicornum Maximowicz* are each cut into pieces, water is added for 2-4 boilings. *Lycium barbarum L.* and *Cuscuta chinensis Lamarck* are each immersed in warm water at 80°-95°C 1-3 times, and after the traditional Chinese medication decoction fluids and warm immersion fluids are blended, the blended mixture is placed in a corresponding large-pore adsorption resin column. When adsorption is complete, water is used to rinse the resin column until the liquid runs clear, followed by elution with 60-80% ethanol. When the runoff becomes darker in color, collection of the eluent is begun, until the color of the eluent turns from dark to extremely light. Water under pressure is used to expel the ethanol from the column, which is then blended with the eluent, the total eluent being approximately 3-8 times the amount of materials by weight. The eluent for each traditional Chinese medication respectively is recovered, concentrated to a 1.10 proportion, and respectively spray-dried to obtain the extract of the various materials. The four extracts are mixed thoroughly and prepared into any clinically acceptable dosage form.

The preferred technical steps for the method of the present invention are below:

2 parts *Tripterygium hypoglaucum (Level) Hutch* by weight

2 parts *Epimedium brevicornum Maximowicz* by weight

1 part *Lycium barbarum L.* by weight

1 part *Cuscuta chinensis Lamarck* by weight

After *Tripterygium hypoglaucum (Level) Hutch* is cut into pieces, 13x, 10x and 10x the amount of water is added for three extractions, 1 h each time. After *Epimedium brevicornum Maximowicz* is cut into sections, 15x, 10x and 10x the amount of water is added for three extractions, 1 h each time. *Lycium barbarum L.* is pulverized to form a crude material, immersed in 20x water at 80°C for 1 h, 3 times in succession. *Cuscuta chinensis Lamarck* is pulverized into a crude powder, immersed in 31x water at 80°C for 1 h, in succession 3 times. The water decoctions or the water immersion liquids of the four materials are filtered separately and passed through a large-pore adsorption resin column JD-1 (WLD). 70% ethanol is used for elution. When the color of the runoff liquid is clearly darker, collection of eluent is started. When the eluent color becomes extremely light the elution is complete. Ethanol is recovered from each eluent of the materials, which is concentrated and dried to finally obtain the extracted materials powders. Each of the four extracted powders of materials is mixed thoroughly and prepared into any clinically acceptable dosage form.

The preparation of the materials in the present invention may further employ the following methods.

The raw materials are weighed, and the *Epimedium brevicornum Maximowicz* and the *Tripterygium hypoglaucum (Level) Hutch* are cut into pieces. The *Lycium barbarum L.* and the *Cuscuta chinensis Lamarck* are in raw form or pulverized, the four ingredients above are each or in combination extracted using 0-95% ethanol at 10-98°C, in succession 1-4 times. After ethanol is recovered from the

extraction fluid separately or in combination, the fluid is concentrated, dried, pulverized, mixed thoroughly or mixed in proportion, to prepare a clinically acceptable dosage form.

Further, the materials of the present invention are formed into active ingredients using the raw materials above.

Of the above-described raw materials, *Epimedium brevicornum Maximowicz* contains *icariine*, *icariside* I, *icariside* II and *icariine* A, *Tripterygium hypoglaucum (Level) Hutch* contains diterpenes, triterpenes and biological alkaloid compounds. The chief components in *Cuscuta chinensis Lamarck* and *Lycium barbarum L.* are flavones.

Thus, preparation of *Epimedium brevicornum Maximowicz* in the present invention can be replaced with one or more of *icariine*, *icariside* I, *icariside* II and *icariine* A. *Tripterygium hypoglaucum (Level) Hutch* can be replaced by the diterpenes, triterpenes and biological alkaloid compounds contained in *Tripterygium hypoglaucum (Level) Hutch*, and *Cuscuta chinensis Lamarck* and *Lycium barbarum L.* can be replaced by their flavone components.

The medication of the present invention (*Fengshiping* capsules) has undergone pharmacodynamic study and it has been proven that when *Fengshiping* is administered by perfusion, it is able to clearly inhibit primary and secondary damage in the rat adjuvant arthritis (AA) model; to clearly inhibit 2,4-dinitrofluorobenzene (DNFB)-induced delayed type hypersensitivity (DTH) in the ear of the mouse; to clearly inhibit hemolysin antibody formation in macrophages in the mouse, spleen cell IL-1, IL-2, IL-6 and TNF activity. *Fengshiping* is able to clearly inhibit ConA-induced lymphocyte transformation, *Fengshiping* is able to clearly inhibit CD_4 and CD_8 cells, although its effect on CD_4 is stronger, it had no clear effect on the CD_4/CD_8 ratio. The above-described *Fengshiping* effects all have a clear, linear dosage-efficacy relationship. 12-18 g/kg (crude drug) is the minimum effective dose. *Fengshiping* also clearly inhibits NK cells. However, *Fengshiping* at effective doses does not cause atrophy of the thymus gland, the spleen and other immunity organs and it also does not inhibit the phagocytic effect of macrophages.

Fengshiping clearly inhibits the inflammation response. It is able to inhibit acetic acid-induced abdominal cavity capillary vessel hyperpermeability in mice; to express croton oil-induced ear inflammation; and carrageenan-induced pleuritis in mice and white blood cell aggregation in CMC sacs in rats. However, *Fengshiping* is weaker in inhibiting carrageenan-induced foot inflammation and granuloma tissue proliferation. In addition to this, *Fengshiping* clearly inhibits the acetic acid-induced body-twisting response in mice.

Experiment 1: Effect on adjuvant arthritis (AA)

1.1 Preventive effect against rat AA.

72 SD isogenous rats, littermates, half male and half female, weighing 180-220 g, were randomly divided into 6 groups, 12 animals per group, in separate cages, 6 animals per cage. Precise narrowband tape measures were used to obtain the rats' left and right rear ankle joint and foot maximum

circumference to serve as the normal value. All were administered by perfusion administration the same volume of different doses of medication or the same volume of an *Astragalus* solution. 1 h after administration, through the left rear foot pad, each group of rats was injected intradermally with 0.1 mL Freund's complete adjuvant per animal. The medication was perfused once a day, for 30 days. The same method was used to obtain the rats' left and right ankle joint and foot circumference. A preventive medication administration test was used to detect daily mouse foot circumference minus the pre-inflammation circumference of the mouse foot to calculate the level of inflammation (Δ cm). The results are shown in Tables 1.1 and 1.2. At the end date, body weight and weight of the main organs were obtained. The results are shown in Tables 1.3 and 1.4.

1.1 Effect of *Fengshiping* on AA mice foot-ankle joint inflammation.

Group	Dose (g/kg)	Level of inflammation (Δ cm)						
		1d	2d	3d	9d	12d	14d	16d
Control	–	0.69 ±0.17	0.69 ±0.12	0.92 ±0.18	0.84 ±0.41	1.10 ±0.30	1.65 ±0.68	2.10 ±0.55
Fengshiping	7.5	0.74 ±0.12	0.66 ±0.074	0.83 ±0.13	0.77 ±0.27	1.11 ±0.45	1.34 ±0.53	1.91 ±0.61
Fengshiping	15	0.80 ±0.24	0.62 ±0.13	0.76 ±0.18	0.49 ±0.17*	0.73 ±0.34*	1.00 ±0.48*	1.38 ±0.67*
Fengshiping	30	0.75 ±0.19	0.67 ±0.19	0.87 ±0.28	0.63 ±0.22	0.73 ±0.34*	0.82 ±0.43**	1.05 ±0.53**
Tripterygium hypoglaucu m (Level) Hutch	5	0.72 ±0.11	0.68 ±0.16	0.91 ±0.18	0.66 ±0.23	0.88 ±0.29	1.03 ±0.36*	1.37 ±0.33*
Prednisone	0.01	0.64 ±0.14	0.64 ±0.16	0.50 ±0.26	0.46 ±0.25	0.72 ±0.46*	0.87 ±0.46**	1.28 ±0.69*

Group	Dose (g/kg)	Level of inflammation (Δ cm)					
		18d	20d	22d	24d	26d	28d
Control	–	2.18 ±0.44	2.05 ±0.46	2.0 ±0.46	2.04 ±0.57	1.92 ±0.65	1.83 ±0.67
Fengshiping	7.5	1.74 ±0.73	1.81 ±0.55	1.81 ±0.52	1.77 ±0.55	1.65 ±0.55	1.55 ±0.49
Fengshiping	15	1.32 ±0.59**	1.28 ±0.58**	1.34 ±0.61*	1.33 ±0.67*	1.20 ±0.64*	1.08 ±0.58**
Fengshiping	30	0.95 ±0.50**	0.87 ±0.51**	0.95 ±0.54**	0.89 ±0.59**	0.90 ±0.57**	0.86 ±0.51**
Tripterygium hypoglaucu m (Level) Hutch	5	1.47 ±0.43**	1.50 ±0.43**	1.49 ±0.43*	1.42 ±0.53*	1.40 ±0.56*	1.32 ±0.57*
Prednisone	0.01	1.18 ±0.7**6	1.03 ±0.67**	1.05 ±0.69*	0.90 ±0.64**	0.86 ±0.65**	0.85 ±0.59**

Compared to control group *P <0.05, ** P< 0.01 (same below)

1.2 Effect of *Fengshiping* on AA mice on the foot-ankle joint inflammation.

Group	Dose (g/kg)	Level of inflammation (Δ cm)					
		2d	9d	12d	14d	16d	18d
Control	–	0.14 ±0.05	0.06 ±0.10	0.34 ±0.36	0.80 ±0.52	1.43 ±0.67	1.36 ±0.61
Fengshiping	7.5	0.18 ±0.06	0.10 ±0.014	0.26 ±0.36	0.82 ±0.52	1.31 ±0.64	1.28 ±0.71
Fengshiping	15	0.15 ±0.08	0.02 ±0.06	0.13 ±0.10*	0.37 ±0.31*	0.90 ±0.56*	0.79 ±0.60*
Fengshiping	30	0.18 ±0.09	0.06 ±0.06	0.16 ±0.08*	0.29 ±0.20**	0.49 ±0.41*	0.33 ±0.29**
Tripterygium hypoglaucu m (Level) Hutch	5	0.16 ±0.07	0.01 ±0.07	0.11 ±0.10	0.44 ±0.19**	0.87 ±0.56*	0.84 ±0.67*
Prednisone	0.01	0.20 ±0.06	0.08 ±0.08	0.21 ±0.16	0.44 ±0.43	0.99 ±0.63	0.84 ±0.74*

Group	Dose (g/kg)	Level of inflammation (Δ cm)				
		20d	22d	24d	26d	28d
Control	–	1.28 ±0.57	1.38 ±0.64	1.35 ±0.75	1.20 ±0.78	1.12 ±0.63
Fengshiping	7.5	1.33 ±0.71	1.31 ±0.73	1.27 ±0.73	1.16 ±0.73	1.07 ±0.65
Fengshiping	15	1.74 ±0.57*	1.92 ±0.61*	0.95 ±0.64*	0.88 ±0.58*	1.83 ±0.55
Fengshiping	30	0.27 ±0.30**	0.34 ±0.31**	0.32 ±0.33**	0.31 ±0.32**	0.34 ±0.32**
Tripterygium hypoglaucum (Level) Hutch	5	0.82 ±0.65*	0.89 ±0.70*	0.80 ±0.67*	0.83 ±0.68**	0.75 ±0.69
Prednisone	0.01	0.82 ±0.72**	0.79 ±0.74*	0.75 ±0.67**	0.68 ±0.64*	0.71 ±0.67

1.3 Effect of *Fengshiping* on AA mice in body weight.

Group	Dose (g/kg)	Change in body weight (g)		
		Initial body weight	AA 1 month body weight	Increase in body weight
Control	–	228 ±34	231 ±52	3
	7.5	229 ±34	220 ±46	-9
Fengshiping	15	223 ±40	232 ±34	9
	30	224 ±37	256 ±60	32
Tripterygium hypoglaucum (Level) Hutch	5	226 ±45	230 ±43	4
Prednisone	0.01	264 ±55	244 ±31	-21

1.4 Effect of *Fengshiping* on AA mice organ weight (preventive).

Group	Dose (g/kg)	Organ system (g tissue/100 g body weight)			
		Liver	Spleen	Thymus gland	Adrenal gland
Control	–	3.92 ±0.65	0.34 ±0.10	0.098 ±0.40	0.027 ±0.01
Fengshiping	7.5	3.73 ±0.29	0.31 ±0.09	0.078 ±0.038	0.027 ±0.008
Fengshiping	15	3.48 ±0.32	0.38 ±0.10	0.100 ±0.034	0.023 ±0.005
Fengshiping	30	3.38 ±0.28*	0.44 ±0.12*	0.100 ±0.032	0.022 ±0.007
Tripterygium hypoglaucum (Level) Hutch	5	3.21 ±0.30**	0.36 ±0.05	0.052 ±0.011**	0.026 ±0.009
Prednisone	0.01	3.04 ±0.20**	0.32 ±0.08	0.050 ±0.060**	0.020 ±0.004*

1.2 Therapeutic effect on AA rats.

50 male SD rats were randomly divided into 5 groups and subjected to the same method. However 13 days after starting injection by perfusion with Freund's adjuvant to induce inflammation, once a day, for 2 weeks, the daily circumference measurement was subtracted from the circumference at the start of medication administration to calculate the level of inflammation (Δ cm). For results see Tables 1.5 and 1.6. For main organ weights see Table 1.7.

1.5. Therapeutic effect of *Fengshiping* on AA rats and foot-ankle joint inflammation.

Group	Dose (g/kg)	Inflammation (Δ cm)			
		1d	2d	4d	6d
Control	–	1.81 ±0.27	1.92 ±0.19	2.12 ±0.22	2.16 ±0.27
Fengshiping	7.5	1.68 ±0.50	1.64 ±0.54	1.70 ±0.57	1.82 ±0.61
Fengshiping	15	1.44 ±0.41*	1.51 ±0.36**	1.65 ±0.34**	1.74 ±0.31**
Fengshiping	30	1.50 ±0.56	1.48 ±0.41**	1.51 ±0.44**	1.59 ±0.51**
Prednisone	0.01	1.78 ±0.51	1.70 ±0.51	1.63 ±0.50*	1.58 ±0.50**

Group	Dose (g/kg)	Inflammation (Δ cm)			
		8d	10d	12d	14d
Control	–	1.92 ±0.32	1.87 ±0.34	1.92 ±0.39	1.78 ±0.44
Fengshiping	7.5	1.67 ±0.68	1.60 ±0.71	1.61 ±0.77	1.58 ±0.71
Fengshiping	15	1.46 ±0.37**	1.48 ±0.30*	1.28 ±0.37**	1.22 ±0.38**
Fengshiping	30	1.29 ±0.58**	1.29 ±0.65**	1.26 ±0.67**	1.20 ±0.68*
Prednisone	0.01	1.27 ±0.46**	1.09 ±0.54**	0.94 ±0.50**	0.94 ±0.42**

1.6. Therapeutic effect of *Fengshiping* on AA rats on opposite side ankle joint inflammation.

Group	Dose (g/kg)	Inflammation (Δ cm) 2d	4d	6d	8d
Control	–	0.36 ±0.26	0.45 ±0.25	0.55 ±0.34	0.47 ±0.29
Fengshiping	7.5	0.12 ±0.25	0.34 ±0.32	0.48 ±0.41	0.28 ±0.38
Fengshiping	15	0.21 ±0.18	0.38 ±0.27	0.44 ±0.33	0.21 ±0.33*
Fengshiping	30	0.10 ±0.48	0.06 ±0.28**	0.11 ±0.24**	0.06 ±0.27**
Prednisone	0.01	0.10 ±0.13*	0.15±0.28*	0.11 ±0.25**	-0.08 ±0.34**

Group	Dose (g/kg)	Inflammation (Δ cm) 10d	12d	14d
Control	–	0.48 ±0.25	0.46 ±0.31	0.40 ±0.36
Fengshiping	7.5	0.35 ±0.30	0.30 ±0.29	0.30 ±0.35
Fengshiping	15	0.19 ±0.45*	0.06 ±0.31**	-0.06 ±0.34**
Fengshiping	30	0.02 ±0.39**	0.05 ±0.38*	-0.02 ±0.41**
Prednisone	0.01	-0.13 ±0.28**	-0.26 ±0.36**	-0.33 ±0.39**

n = 10, compared to control group, *P < 0.05, ** P < 0.01

1.7 Effect of *Fengshiping* on AA rat body weight and immune system organ weight.

Group	Dose (g/kg)	Organ index (g tissue/100 g body weight) Liver	Spleen	Thymus gland	Adrenal gland
Control	–	0.35 ±0.23	0.35 ±0.061	0.078 ±0.014	0.026 ±0.0071
Fengshiping	7.5	3.21 ±0.52	0.33 ±0.091	0.071 ±0.026	0.024 ±0.0085
Fengshiping	15	3.40 ±0.54	0.36 ±0.014	0.067 ±0.022	0.023 ±0.0048
Fengshiping	30	2.79 ±0.43	0.32 ±0.014	0.069 ±0.029	0.023 ±0.0072
Tripterygium hypoglaucum (Level) Hutch	5	3.92 ±0.59	0.35 ±0.083	0.075 ±0.034	0.027 ±0.0060
Prednisone	0.01	3.52 ±0.35	0.28 ±0.047*	0.05 ±0.011**	0.02 ±0.0043*

From Tables 1.1, 1.2, 1.3, 1.5 and 1.6 it can be seen that *Fengshiping* had a strong inhibitory effect on primary damage from the adjuvant arthritis rat model at the injection side and secondary joint damage on the opposite side. At the time of induced inflammation and 2 weeks after induced inflammation, medication administration gave clear results, demonstrating that *Fengshiping* had a clear preventive and therapeutic effect on adjuvant arthritis in the rat. Comparison of the effect of *Fengshiping* on rat rear limb-ankle joint specific immunity inflammation and mouse foot non-specific inflammation shows that *Fengshiping* effect on ankle joint inflammation was strong, demonstrating the main effect of *Fengshiping* in inhibiting the immunity inflammation response.

The results in Tables 1.3, 1.4 and 1.7 demonstrate that, throughout the experimental period, the AA rats showed no clear increase in body weight, and when *Fengshiping* was at the effective dose, rat body weight increased. In the prednisone therapy and prevention group all rat body weights declined, and the thymus gland and the adrenal gland clearly atrophied. In *Tripterygium hypoglaucum (Level) Hutch* alone, thymus gland atrophy could also be seen, however, the three *Fengshiping* doses did not appear to have a clear effect on thymus gland and adrenal gland weight.

1.3. Pathological changes in AA rat model after treatment

45 SD rats were divided into 6 groups, weight 180 20 g. After Freund's adjuvant was used to cause AA, *Fengshiping* by perfusion was administered for 5 days. 1 h after the final administration, evaluation was performed and the rat arthritis index was calculated. Secondary damage to the rat on the side of the rear limb joint was fixed using formaldehyde, and stained with HE, and changes to joint synovial membrane and cartilage were observed under microscope. Rat joint index results for each group are shown in Table 1.8.

1.8 *Fengshiping* effect on AA rat joint index.

Group	Dose (g/kg)	Number of rats (per group)	Joint index
Control group	–	8	0**
AA model group	–	7	6.2 ±0.49
Fengshiping	7.5	9	4.86 ±0.90**
Fengshiping	15	7	4.71 ±0.95**
Fengshiping	30	7	4.56 ±1.13**
Tripterygium wilfordii polyglucoside	0.006	7	4.57 ±0.79**

Compared to model group **P < 0.01

The joint index was scored based on redness and inflammation of each joint of the rat, from 0-4 points. The four limb scores were totaled to create the joint index. The four limbs and the joint scoring standards follow: 0 points = normal, 1 point = redness only, 2 points = redness and mild inflammation, 3 points = severe inflammation, 4 points = joint deformation and rigidity.

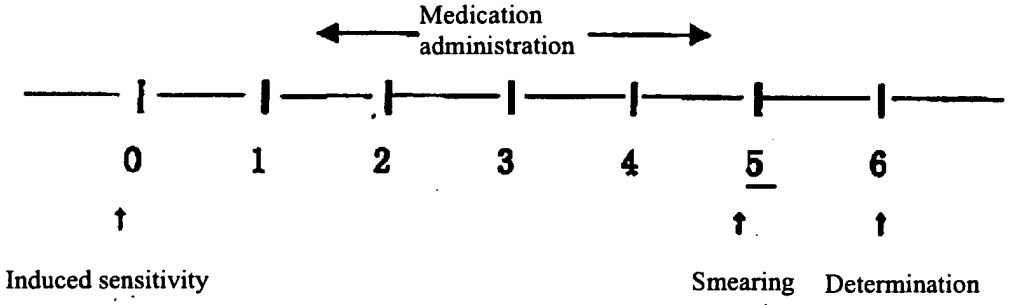
Under a microscope, it could be observed that the rats in the model group in which the rear limb joint synovial membrane had grown, collagen fibers had increased, lymphocytes and plasma cells had infiltrated, a clear granuloma formed. The synovial membrane cells degenerated, the cytoplasm stained red, the cell nucleus had undergone pycnosis, in some areas the synovial membrane epidermis had worn away, the cartilage atrophied, the surface being rough, bumpy and uneven, and there was a slight increase in cartilage cells. After treatment with the various *Fengshiping* dose groups, joint synovial membrane tissue inflammation was lessened and more collagen fibers formed. The synovial membrane cells were less worn away, cartilage surface cells increased, the surface was smoothened, and the cartilage was recovering.

In control group rats, proliferation of synovial membrane layers could be seen. There was increased collagen fiber and lymphocyte and plasma cell infiltration, the formation of a clear granuloma, synovial cell degeneration, red staining of the cytoplasm, cell nucleus pycnosis, and in some areas synovial epidermis was worn away. In the *Fengshiping* treatment group, joint synovial tissue inflammation was lessened, more collagen fibers formed, synovial membrane cells were less worn away, cartilage surface cells increased, the surface smoothened and the cartilage was in recovery.

Experiment 2. 50 NIH mice with 2,4-dinitrofluorobenzene (DNFB)-induced delayed type hypersensitivity (DTH) reaction in the ear, half male and half female, were randomly divided into 5 groups. A 0.025 mL 1% DNFB acetone solution was applied to sites with the abdominal hair removed to induce sensitivity. On alternate days, the same method was used to intensify one time, and on the fifth day after sensitivity was induced a 0.01 mL 1% DNFB food oil solution was smeared on the right ear of the animal, at 24 h the mouse was sacrificed. A balanced twisting force was used equally on the left and the right ears to determine the difference in weight (mg) between the two, which served as the mouse's DTH reaction intensity. The experiment was carried out on the different immunities and administration methods.

2.1 Effect of full course administration on DTH

The immunity and medication administration procedures are below:



2.1 Effect of *Fengshiping* on NIH mouse DNFB-induced delayed type hypersensitivity reaction.

Group	Dose (g/kg)	Administration Time	Number of mice (per group)	Ear inflammation percentage	Inhibition rate	P value
Control			10	34.20±3.77		
Fengshiping	27	0-5	10	26.24±3.34	23.3	<0.01
Fengshiping	40	0-5	10	12.99±4.96	62.0	<0.01
Fengshiping	60	0-5	10	10.43±7.53	69.5	<0.01
Dexamethasone	0.003	0-5	10	13.93±4.41	59.3	<0.01
Control			10	42.43±5.28		
Fengshiping	40	-2-0	10	31.50±10.52	25.0	<0.01
Fengshiping	40	-2-2	10	30.88±7.92	27.2	<0.01
Fengshiping	40	-2-5	10	21.07±4.62*	50.3	<0.01
Fengshiping	40	-5-6	10	32.00±9.37	41.7	<0.01
Cyclophosphamide	0.05	-2-2	10	39.40±10.78	8.1	<0.05
Cyclophosphamide	0.05	-2-0	10	37.47±6.71	11.7	<0.05
Control			10	38.50±4.67		
Cy	0.1 *3	Once, days 0, 2, 4	10	23.00±7.65	40.3	<0.01
Cy	0.25	-3d	10	41.84±7.75	-8.7	
Fengshiping	60	0-4	10	27.20±10.20	29.4	<0.01
Cy + *Fengshiping*	0.25 + 60	-3,0-4	10	38.07±6.65	1.1	

* Compared to the various other groups $P < 0.05$ or $P < 0.01$

From the results in Table 2.1 it can be seen that *Fengshiping* has a clear inhibitory effect on DNFB-induced murine DTH, and the intensity of its inhibitory effect has a clear dose relationship. A larger dose gives a stronger effect, at 60.9 g/kg it can cause the DTH inhibition rate to reach 69.5%.

2.2 Effect of different medication administration times on murine DTH

Immunity and medication administration procedures and results can be seen in the center columns and lower columns of Table 2.1. The table's center columns show 2 days before and the day sensitivity was induced, 2 days before sensitivity was induced to 2 days after sensitivity was induced, 2 days before sensitivity was induced to 5 days after sensitivity was induced, and medication administered before and after the smearing. In all cases the murine DTH reaction was inhibited, however the inhibitory effect was especially strong prior to inducing sensitivity and after inducing sensitivity; the entire medication administration procedure—that is, administration 2 days before inducing sensitivity to 5 days after inducing sensitivity, indicates that *Fengshiping* inhibition of the DTH effect and the mechanism may also be related to inhibition of the DTH reaction's early-stage participation in the cells and related to inhibition of DTH late-stage effective cells and DTH reaction mid-stage cells, different from cyclophosphamide. When cyclophosphamide was administered 2 days prior to induced sensitivity until the day sensitivity was induced or 2 days after induced sensitivity, smaller doses did not affect the DTH reaction.

From the lower columns of Table 2.1 it can be seen that when a single large dose of cyclophosphamide was administered three days before sensitivity was induced, intense inhibition of Ts cells made Th cells relatively hyperfunctional, which showed that not only did it not inhibit the murine DTH reaction, on the contrary, there was increased strength. At this point if it were to be used with *Fengshiping*, which has clear DTH inhibition results, the inhibition efficacy of *Fengshiping* would be cancelled out, which shows that the mechanism of effect of *Fengshiping* inhibition of the DTH reaction differs from that of cyclophosphamide and may be relatively sensitive to the inhibitory effect against TH cells.

Experiment 3. Effect on humoral immunity

3.1 Effect on chicken red blood cell (CRBC) immunity induced in normal murine hemolysin antibody formation

190 mice of 18-22 g, half male and half female, were randomly divided into 19 groups. Each group was immunized with 0.2 mL IP 5% CRBC. At 7 days after immunization, blood was taken from the eyeballs. After dilution with physiological saline, the effect of *Fengshiping* on murine hemolysin antibodies was determined for each group of mice. *Fengshiping* immunity perfusion started at different times. The results are shown in Tables 3.1, 3.2 and 3.3.

Table 3.1. Effect of *Fengshiping* on NIH murine hemolysin antibody formation

Group	Dose (g/kg)	Medication administration time	Number of mice (per group)	Hemolysin value	Inhibition rate	P value
Control			10	169.0 ±62.0		
Fengshiping	18	0-7	10	46.0 ±15.6	72.8	<0.01
Fengshiping	27	0-7	10	35.4 ±12.0	79.1	<0.01
Fengshiping	40	0-7	10	28.2 ±5.9	83.3	<0.01
Fengshiping	60	0-7	10	16.7 ±3.0	90.1	<0.01
Tripterygium hypoglaucum (Level) Hutch	13.3	0-7	10	121.0 ±88.0**	28.4	<0.015
Cyclophosphamide	0.02	0-7	10	35.0 ±12.0	79.3	<0.01

** Compared to *Fengshiping* containing identical *Tripterygium hypoglaucum (Level) Hutch* (40 g/kg) $P < 0.01$

Table 3.2. Effect of *Fengshiping* on ICR murine hemolysin antibody formation

Group	Dose (g/kg)	Medication administration time	Number of mice (per group)	Hemolysin value	Inhibition rate	P value
Control	–	–	10	124.70 ±2.60		
Fengshiping	12	0-7	10	75.00 ±53.10	39.9	<0.05
Fengshiping	18	0-7	10	45.60 ±22.70	63.4	<0.01
Fengshiping	27	0-7	10	29.10 ±22.10	76.8	<0.01
Fengshiping	40	0-7	10	28.20 ±5.30	77.4	<0.01
Tripterygium hypoglaucum (Level) Hutch	6.0	0-7	10	143.50 ±67.90**		>0.05
Cyclophosphamide	0.02	0-7	10	27.80 ±6.60	77.9	<0.01

Compared to *Fengshiping* identical dose (18 g/kg) $P < 0.01$

Table 3.3. Effect of *Fengshiping* on ICR murine hemolysin antibody formation

Group	Dose (g/kg)	Medication administration time	Number of mice (per group)	Hemolysin value	Inhibition rate	P value
Control	–	–	10	256.0 ±26.0		
Fengshiping	18	-7-7	10	198.0 ±50.0	22.7	<0.01
Fengshiping	18	-3-7	10	156.0 ±85.0	39.1	<0.01
Fengshiping	18	0-7	10	98.0 ±35.0	61.7	<0.01
Cyclophosphamide	0.02	0-7	10	25.0 ±4.0	90.2	<0.01

From the results in the three tables above it can be seen that *Fengshiping* creates a clear inhibitory effect on hemolysin antibodies in different strains of mice, and as the dose is increased the effect is strengthened; it has a good dose—efficacy relationship. The lowest inhibition dose is 12 g/kg, compared to the *Fengshiping* group formed from *Tripterygium hypoglaucum (Level) Hutch* as one of the chief components, the inhibitory effect created against the antibody is clearly strong. The results in Table 3.1 show that the intensity of *Fengshiping*'s effect is about 2.25 times or higher (effect of 13.5 kg *Tripterygium hypoglaucum (Level) Hutch* is weak compared to the effect of *Fengshiping* containing 6 g/kg *Tripterygium hypoglaucum (Level) Hutch*).

3.2 Effect on AA mouse humoral immune function

The right rear foot metatarsal of NIH mice, weighing 20 ±2 g, was intradermally injected with

0.05 mL of Freund's complete adjuvant. after 3 weeks an AA mouse model was created, after they were randomly divided into 6 groups, each mouse was perfused with different medications for 5 days. at the start of administering medication at the same time, 0.5 mL IP 10% sheep red blood cells (SRBC) was administered to induce sensitivity. after 5 days the mice were sacrificed, the spleens obtained and after rinsing in Hank's solution, a lymphocyte suspension was prepared. The cell concentration was adjusted to 2×10^7/mL, 1 mL added to test tubes, 1 mL 0.2% SRBC and 1 mL 1:30 complement added, followed by incubation in a 37°C water bath for 1 h and centrifugation at 2000rpm for 5 min. the supernatant was obtained, and 722 spectrophotometry was used to count at a wavelength at 415 nm to detect the optical density and represent the PFC count.

Blood was obtained from the sensitivity-induced mice, the serum was separated, and an agglutination test used to determine the antibody efficacy value, expressed using a Log2 value. The results are shown in Table 3.4.

Table 3.4 Effect of *Fengshiping* on AA mouse humoral immune function

Group	Dose (g/kg)	Medication administration time	PFC (OD)	IgM(Log_2)
Control group	–	8	0.819 ±0.013#	6.875 ±0.641
AA model control group	–	10	0.940 ±0.019**	7.700 ±0.599*
Fengshiping	5	8	0.834 ±0.012**#	6.875 ±0.641#
Fengshiping	10	8	0.834 ±0.12**#	6.750 ±0.886#
Fengshiping	20	8	0.830 ±0.014**#	6.375 ±0.518##
Tripterygium wilfordii polyglucoside	0.012	10	0.835 ±0.015**#	6.950 ±0.597#

Compared to the control group * P <0.05, ** P <0.01; compared to the model group # P <0.05, ## P <0.01

From Table 3.4 it can be seen that AA mouse PFC and IgM are clearly higher than in normal mice, and *Fengshiping* is clearly able to reduce AA mouse spleen antibody formation cells (PFC) and antibody (IgM) formation.

Experiment 4. Effect on rat passive cutaneous anaphylactic (PCA) reaction.

Rats received a muscular injection of 10 mg/kg egg albumin. at the same time they were immunized by abdominal cavity injection of 0.2 mL 2×10^{10}/mL *Bordetella pertussis*. After two weeks the rats were sacrificed and exsanguinated. The serum was segregated to make ready for use.

60 rats weighing 150-200 g, half male and half female, were randomly divided into 6 groups. They were lightly anesthetized under ether at a dorsal site with the fur shaved away and intradermally injected with 0.1 mL of the above-described egg albumin serum (diluted 1:5 and 1:10, each labeled d_1, d_2); each dilution degree was 2 points. After 48 h, 1 mg 0.5% Evans blue physiological saline solution containing egg albumin in 1 mL IV was administered. After 20 min the rat was sacrificed by decapitation and its dorsal skin was turned back. Based on the nucleus ceruleus color intensity and area, dye exudation intensity was used to evaluate the nucleus ceruleus grade. then the blue-dyed skin was cut into pieces, immersed in 5 M 10.1% acetone sulfate (7:3) solution, centrifuged after 48 h, and the supernatant optical

density was measured at 590 nm to calculate the PCA reaction strength and inhibition percentage for the various rat groups. The results are shown in Table 4.

Table 4. Effect of *Fengshiping* on rat PCA

Group	Dose (g/kg)	Subvalue		Absorbance	
		Liver	Spleen	Thymus gland	Adrenal gland
Control	–	5.60 ±1.78	2.40 ±2.46	0.191 ±0.129	0.096 ±0.106
Fengshiping	12	7.50 ±2.51	4.20 ±2.49	0.402 ±0.213*	0.192 ±0.175
Fengshiping	24	7.10 ±2.13	4.10 ±1.79	0.310±0.177	0.137 ±0.099
Fengshiping	48	6.00 ±1.83	1.70 ±1.95	0.121 ±0.109	0.024 ±0.026*
Tripterygium hypoglaucum (Level) Hutch	8	6.11 ±1.27	2.56 ±1.67	0.223 ±0.122	0.074 ±0.045
Ketotifen	0.1	2.78 ±1.64**	0.67 ±1.41	0.033 ±0.024**	0.027 ±0.019*

Compared to control group *P <0.05, **P <0.01

It can be seen in Table 4 that *Fengshiping*'s inhibitory effect on rat PCA is weak and it is only at large doses that there is a clear difference compared to the control.

Experiment 5. Effect on cytokines.

5.1 Effect on murine TNFα and IL-2

60 ICR mice weighing 18-22 g, half male and half female, were randomly divided into 6 groups, each perfused with different doses of *Fengshiping* or other medications, once per day for 10 days. 24 h after the final dose of medication, under sterile conditions, mice peritoneal cavity macrophages or spleen cells were taken and Hank's solution was used to wash twice. washing was performed once using serum-free RPMI 1640 solution, the cell suspension was adjusted to 2×10^8/mL using a 5% FCS-RPMI 1640 solution, LPS 10 ng/mL or 10 ng/mL Con A was added, respectively, and culture was carried out for 48 h at 37°C under 5% CO_2. TNFα or IL-2 was detected.

TNFα determination:

On a murine anti-TNFα monoclonal antibody plate, after restoring to room temperature, 50 μL/well of culture supernatant was added. After 60 min, biotin-labeled antibody was added. After 2 h at 25°C, enzyme-carrying avidin added. After 30 min a stop solution was added. The OD value was detected at 450 nm wavelength. According to the OD value on the standard curve, TNF-α level (ng/mL) was calculated.

IL-2 determination:

Logarithmic formation phase IL-2 formation-dependent CTLL cells were adjusted using 5% FCS-RPMI 1640 to form a 1×10^5/L cell suspension. To the 96-well flat bottom cell culture plate were added a 100 μL/well CTLL cell suspension and 100μl/well culture supernatant solution. each sample was repeated in 3 wells, at the same time different dilution strength standard rHIL-2 and culture solution controls were performed. At 37°C and under 5% CO_2 culture was performed for 24 h, followed by

centrifugation at 6 h before the culture was interrupted. 110 μL/well supernatant was removed, 10 μL/well of MTT added, and after 3 h at 37°C, OD 570 nm and 630 nm values were detected, for each well OD value = OD 570 nm—OD 630 nm.

$$\text{IL-2 activity} = \frac{\text{Sample } \overline{OD} - \text{culture solution control } \overline{OD}}{\text{Standard product } \overline{OD} - \text{culture solution control } \overline{OD}} \times \text{standard product activity unit (IU/mL)}$$

Table 5.1. Effect of *Fengshiping* on TNF and IL-2

Drug reference	Dose (g/kg)	Number of mice (per group)	TNF (pg/mL)	IL-2 (IU/mL)
Control group	–	10	87.80 ±14.63	26.30 ±4.22
Fengshiping	12	10	62.14 ±13.13**	16.00 ±2.89**
	24	10	58.60 ±9.63**	18.80 ±2.86**
	36	10	54.40 ±10.88**	18.20 ±2.86**
Tripterygium wilfordii polyglucoside	8	10	58.25 ±10.32**	16.00 ±2.88**
Cyclophosphamide	0.02	10	42.20 ±9.57**	10.10 ±3.08**

*P <0.05, **P <0.01

The results in Table 5.1 show that *Fengshiping* has a clear inhibition effect on TNFα. At 12 g/kg it can be seen to have an extremely clear inhibitory effect; the larger the dose the stronger the effect, however the dose—efficacy curve is level. For IL-2, *Fengshiping* also has a clear inhibitory effect, but the dose—efficacy relationship is unclear.

5.2 Effect on IL-1 and IL-6.

70 NIH mice weighing 18-22 g, half male and half female, were randomly divided into 7 groups, each perfused with different doses of *Fengshiping* or other medications, once per day for 10 days, and sacrificed 24 h after the final medication was administered. The methodology described below was used to detect IL-1 and IL-6 for abdominal cavity macrophages and spleen cells.

IL-1 detection:

Under sterile conditions, abdominal cavity macrophages were obtained, washed twice with Hank's solution, washed once with serum-free RPMI 1640, adjusted with 5% FCS-RPMI 1640 to form a

4×10^6/mL cell suspension; 1 mL was placed in a Kahn tube, cultured for 1 h at 37°C under 5% CO_2, and non-adhered cells removed. 5% FCS-RPMI 1640 and LPS (10 ng/mL) were added, followed by culturing for 72 h at 37°C under 5% CO_2, and repeated freezing and thawing, and then storage at 4°C. Separately, C57 mice were obtained, and thymus gland cells were removed under sterile conditions and adjusted with 5% FCS-RPMI 1640 to form a 1×10^5/mL cell suspension.

100 μL each of the thymus gland cell suspension and frozen and thawed supernatant was added to a 96-well, flat bottom cell culture plate, three wells for each sample, at the same time different dilutions of standard product rHIL-1 and culture solution served as a control. Then 2 ng/well of Con A was added and the plate was placed at 37°C under 5% CO_2 for 72 h. 14 h before the culture was interrupted, 0.1 μCi/well ^{3}H-TdR was added and a multi-head cell collection device to collect the cells and detect the cpm value.

$$\text{IL-1 activity} = \frac{\text{Sample } \overline{\text{cpm}} - \text{culture solution control } \overline{\text{cpm}}}{\text{Standard product } \overline{\text{cpm}} - \text{culture solution control } \overline{\text{cpm}}} \times \text{standard product activity unit (ng/mL)}$$

IL-6 detection:

Under sterile conditions, murine spleen cells were obtained, washed twice with Hank's solution, washed with serum-free RPMI 1640 once, and adjusted with 5% FC-RPMI 1640 to form a 2×10^6/mL cell suspension. 1 mL was placed in a Kahn tube, ConA (10 ng/mL) was added, and culturing was performed for 72 h at 37°C under 5% CO_2 conditions.

Logarithmic formation phase IL-6 dependent formation MH60 cells were adjusted with 5% FC-RPMI 1640 to form a 1×10^5/mL cell suspension.

100μl/well of MH60 cell suspension was added to a 96-well, flat bottom cell culture plate, 25 μL/well of culture supernatant, 200 μL/well of 5% FCS-RPMI 1640 were added to make up the deficiency, three wells for each sample. At the same time, different dilutions of standard rHIL-6 and culture solution control were produced. It was cultured at 37°C under 5% CO_2 for 72 h, 6 h before the culture was interrupted it was centrifuged, 110 μL/well of supernatant obtained, MTT 10 μL/well added, at 37°C for 3 h, OD570nm and OD630 nm values detected, for each well OD value = OD570 nm—OD630 nm.

$$\text{IL-2 activity} = \frac{\text{Sample } \overline{OD} - \text{culture solution control } \overline{OD}}{\text{Standard product } \overline{OD} - \text{culture solution control } \overline{OD}} \times \text{sample dilution} \times \text{standard product activity unit (IU/mL)}$$

5.2. Effect on murine IL-1 and IL-6.

Drug reference	Dose (g/kg)	Number of mice (per group)	IL-1 (ng/mL)	IL-6 (IU/mL)
Control group	–	10	78.7 ±7.1	94.6 ±6.8
	7.5	10	59.3 ±4.9**	64.9 ±4.8*
Fengshiping	15	10	53.3 ±5.7**	60.5 ±4.3**
	30	10	54.4 ±4.8**	56.0 ±4.6
	60	10	47.0 ±16.6*	56.6 ±6.1**
Tripterygium hypoglaucum (Level) Hutch	5	10	57.6 ±4.7**	65.7 ±4.9**
Cyclophosphamide	0.02	9	44.5 ±7.7	49.6 ±6.7**

From the table it can be seen that *Fengshiping* has a strong inhibitory effect on mice abdominal cavity macrophage formation IL-1 and spleen cell formation IL-6, and as the dose increases the effect increases.

5.3 Effect on plasma NO in adjuvant arthritis in rats

60 SD rats weighing 160-200 g, half male and half female, were randomly divided into 6 groups; in the blank control group, the right rear foot metatarsal of each rat was intradermally injected with 0.5 mL NS. In the model group and the *Fengshiping* high, middle and low dose groups and the *Tripterygium wilfordii* polyglucoside group, the right rear foot metatarsal of each rat was intradermally injected with 0.5 mL Freund's complete adjuvant (FCA). After 18 days the rat adjuvant arthritis model had been created, and gravage administration of medication was started, once per day for five days. The blank control group and the model group were administered distilled water. The high, medium and low dose groups, respectively, were administered high, medium and low doses of *Fengshiping*, and the positive control group was administered *Tripterygium wilfordii* polyglucoside tablets. One hour after the final dose of medication, 2 mL of blood was taken from the abdominal aorta, the plasma was separated and stored at -70°C for future testing. NO determination was performed according to the instructions in the NO reagent kit: 0.6 mL reagent C was added to 0.1 mL plasma and mixed thoroughly, 0.4 mL double-distilled water was added, mixed thoroughly, 0.1 mL reagent D added and mixed thoroughly, incubated on ice for 60 min, centrifuged at 12,000 rpm for 2 min, 0.4 mL double-distilled water and 0.1 mL reagent A added to 0.6 mL supernatant; after incubation on ice for 15 min, 0.1 mL reagent B was added, it was placed at room temperature for 1 h, and at 545 nm the specific color OD value was determined. According to the sample's OD value, the standard curve was used to calculate NO levels. The results can be seen in Table 5.3.

Table 5.3. Effect of *Fengshiping* on adjuvant arthritis rat plasma NO

Drug reference	Dose (g/kg)	Number of mice (per group)	NO level (μ mol/L)	y (y-ILgx)
Control group	–	8	13.55 ±1.11*	1.131 ±0.032
AA model group	–	9	17.56 ±4.15**	1.235 ±0.097
Fengshiping	12	7	9.83 ±2.58**ΔΔ	0.985 ±0.087
Fengshiping	24	7	10.12 ±1.56**ΔΔ	1.001 ±0.067
Fengshiping	48	7	10.70 ±1.51**ΔΔ	1..026 ±0.062
Tripterygium wilfordii polyglucoside	0.006	7	15.25 ±3.48	1.173 ±0.099

Compared to the model group *P <0.05, **P <0.01; compared to *Tripterygium wilfordii* polyglucoside ΔΔ P <0.01

From Table 5.3 it can be seen that the rat plasma NO level in the model group is clearly higher than in the blank control group and *Fengshiping* is clearly able to reduce AA rat plasma NO levels. *Tripterygium wilfordii* polyglucoside tablets are also able to reduce arthritic rat plasma NO levels; however the effect is clearly weak.

Experiment 6. Effect on murine T lymphocytes, CD_4, CD_8 and NK cells.

6.1. Effect on normal murine lymphocyte conversion

80 NIH mice, half male and half female, were randomly divided into 8 groups, perfused with different medications, once per day for 10 days. 24 h after the final dose of medication, the mice were sacrificed, and under sterile conditions murine spleen cells were obtained, washed twice with Hank's solution, washed once with serum-free RPMI 1640, and adjusted with 5% FCS-RPMI 1640 to form a 2×10^6/mL cell suspension. The cell suspension was added to a 96-well flat bottom cell culture plate, 100g μL/well, 3 wells each part, to which stimulant (ConA 2 ng/well) was added to 2 wells to serve as conversion wells, additionally 1 well had no stimulant added and served as a control well. The plate was placed at 37°C under 5% CO_2 to culture for 72 h. 14 h before the culture was interrupted, 0.1 μCi/well ^{3}H-TdR was added. A multi-head cell collection device was used to collect cells, the cpm values were detected and the average value calculated for the multiple wells. Each group's cpm or stimulation index was used directly to perform the comparison. The stimulation index was calculated using the formula below:

$$\text{Stimulation index} = \frac{(\text{Stimulation } \overline{\text{cpm}})}{(\text{Control } \overline{\text{cpm}})}$$

See Table 6.1 for results.

Table 6.1. Effect on ConA-induced murine lymphocyte conversion

Drug reference	Dose (g/kg)	Number of mice (per group)	cpm	Stimulation index
Control	–	10	20433 ±3579	25.87 ±3.06
	7.5	10	13566 ±1779**	27.29 ±7.67
	15	10	12708 ±1692**	18.04 ±3.76
Fengshiping	30	10	12809 ±2575**	16.17 ±4.37
	60	10	12090 ±1706**	19.05 ±3.80
	2.5	10	18038 ±3359	17.11 ±2.60
Tripterygium hypoglaucum (Level) Hutch	5	10	12081 ±1039**	17.58 ±4.37
Cyclophosphamide	0.02	9	9922 ±1145**	13.66 ±2.28

Compared to the control *P <0.05, **P <0.01

From Table 6.1 it can be seen that *Fengshiping* has a clear inhibitory effect on ConA-induced lymphocyte conversion and shows a definite dose—efficacy relationship.

6.2. Effect on normal murine CD_4, CD_8 and NK cells.

The same experiment as in 5.1 was conducted. 24 h after medication was terminated, 5% FCS-RPMI 1640 was used to prepare a murine spleen cell suspension, the cell count was adjusted to 2×10^8/mL and CD_4, CD_8, and their ratio and NK cells were determined.

Determination of CD_4 and CD_8:

A 50 μL murine spleen cell suspension was added to polylysine-coated glass slides to prepare a cell smear. Murine T cells were used as the positive control. After the cell smear was fixed with acetone, normal murine serum was used to seal, human biotin-labeled anti-CD_4 and CD_8 antibodies were added, followed by incubation at 37°C for 2 h. enzyme-carrying avidin was added, placed at room temperature for 10 min, substrate added for 10 min, washed, and hematoxylin counter-staining was performed for 2 min. After gradient alcohol dehydration, gelatin glycerin was used to seal the slides, and 200 cells were counted under a high-magnification microscope.

$$\text{Cell level} = \frac{\text{Color cell count}}{200} \times 100\ \%$$

NK cell determination:

EC cell preparation: Under sterile conditions, murine spleen cells were obtained, washed with Hank's solution twice, washed once with serum-free RPMI 1640, and adjusted using 5% FCS-RPMI 1640 to form a 2×10^8/mL cell suspension, to serve as EC.

TC cell preparation: Logarithmic growth phase murine NK cell-sensitive Yack-1 cells were adjusted to form a 4×10^4/mL cell suspension, to serve as TC.

Determination: 100 μL each of EC and TC were added to a 96-well flat bottom cell culture plate, 3 duplicate wells per sample, at the same time EC and TC served as controls (EC control: 100 μL EC + 100 μL 5% FCS RPMI 1640; TC control: 100 μL TC + 100 μL 5% FCS RPMI 1640). At 37°C and 5% CO_2 conditions, culture was performed for 24 h; 6 h before the culture was interrupted it was centrifuged, 110 μL/well supernatant removed, MTT 10 μL/well added, OD570 nm and OD630 nm values detected at 37°C for 3 h, OD value = OD570 nm—OD630 nm per well.

$$\text{NK activity} = \frac{(1 - \frac{\text{Sample } \overline{OD} - \text{EC control } \overline{OD}}{\text{TC control } \overline{OD}})}{} \times 100\ \%$$

Table 6.2 Effect of *Fengshiping* on CD_4, CD_8 and NK cells

Group	Dose (g/kg)	Number of mice (per group)	CD_4 (%)	CD_8 (%)	CD_4/CD_8	NK
Control	–	10	20.80 ±2.94	14.80 ±2.49	1.42 ±0.18	40.13 ±4.89
	12	10	19.14 ±2.91	13.43 ±2.51	1.43 ±0.08	31.94 ±4.52**ΔΔ
Fengshiping	24	10	17.30 ±2.51**	12.00 ±2.40	1.46 ±0.16	35.36 ±3.40*ΔΔ
	36	10	16.30 ±2.50**	11.23 ±2.94**	1.49 ±0.20	31.06 ±3.53**ΔΔ
Tripterygium hypoglaucum (Level) Hutch	8	10	16.25 ±2.25**	11.50 ±2.45	1.44 ±0.18	32.20 ±2.00**
Cyclophosphamide	0.02	10	11.50 ±2.50**	4.10 ±1.20**	2.91 ±0.53**	23.10 ±3.66**

Compared to the control group *P <0.05, **P <0.01; compared to cy ··P <0.01

From Table 6.2 it can be seen that *Fengshiping* had a definite inhibitory effect on CD_4 and CD_8 cells and also presented a dose – efficacy relationship. however the dose – efficacy curve was level. For CD_4 inhibition, the effective dose was 24 g/kg, and for CD_8 cells thus it was only the 36 g/kg high dose that had a clear inhibitory effect. Correspondingly, *Fengshiping* had no clear effect on the CD_4/CD_8 ratio. Cyclophosphamide then had a strong inhibitory effect on CD_4 and CD_8 and the effect on CD_8 was especially strong. These results caused a greater increase in CD_4/CD_8 ratio.

Fengshiping also had clear inhibition against NK cells. However, the dose – efficacy relationship was not clear. Cyclophosphamide had an intense inhibitory effect, 20 mg/kg was compared to the effect of 12, 24, and 36 g/kg *Fengshiping*, and for all there was an extremely clear difference.

6.3. Effect on AA murine lymphocyte count and function.

20 ± 2 g NIH mice were each intradermally injected at the rear right foot metatarsal with 0.05 mL Freund's complete adjuvant, and after three weeks an adjuvant arthritis model was ready. In the negative control group, the rear right foot metatarsal of each mouse was intradermally injected with 0.05 mL physiological saline. Medication was administered via perfusion, once per day for 5 days. After 5 days, peripheral blood slides were prepared for each group of mice to perform esterase staining. Under an oil immersion microscope the esterase stain positive cell percentage (i.e., peripheral blood T cell percentage) was measured. After the mice were anesthetized, the spleen was prepared into a monocyte suspension, washed with PBS once, the supernatant removed, and 4 mL of red cell solution added; after shaking for 2-3 min for complete red cell lysis, it was centrifuged to remove the supernatant, and washed twice with fluorescence wash solution. After it was centrifuged, the supernatant was removed and cell concentration was adjusted to 1×10^6/mL. To each tube were added 50 μL of diluted anti-CD_4 and CD_8 antibodies, followed by incubation at 4°C for 1 h. After it was washed twice with fluorescence wash solution 2 mL of fixing solution was added. A 400-mesh filter was used to filter into a FCA tube and an upflow-style cell instrument was used for analysis. The results can be seen in Table 6.3.

Table 6.3. Effect on adjuvant arthritis murine T cells

Group	Dose (g/kg)	ANAE+ (%)	CD4+ (%)	CD8 (%)	CD4+/CD8+
Control group	–	50.60 ±4.25	26.13 ±1.16	15.56 ±0.68	1.68 ±0.08
AA Model group	–	49.00 ±4.22$^{\Delta}$	32.56 ±2.87**	13.59 ±1.03**	2.49 ±0.16**
	7.5	49.13 ±4.03$^{\Delta}$	27.30 ±1.76##$^{\Delta}$	15.98 ±1.11##$^{\Delta}$	1.71 ±0.04##$^{\Delta}$
Fengshiping	15	49.31 ±3.29$^{\Delta}$	27.96 ±1.67##$^{\Delta}$	16.23 ±1.27##$^{\Delta}$	1.73 ±0.05##$^{\Delta}$
	30	48.56 ±3.23$^{\Delta}$	26.75 ±1.94##$^{\Delta}$	15.58 ±1.29##$^{\Delta}$	1.72 ±0.04##$^{\Delta}$
Tripterygium wilfordii polyglucoside	0.012	48.88 ±2.89$^{\Delta}$	27.88 ±1.99##$^{\Delta}$	16.33 ±1.31##$^{\Delta}$	1.70 ±0.03##$^{\Delta}$

n = 8, compared to the control group *P <0.05, **P <0.01. compared to the model group #P <0.05, ##P <0.01. compared to the control group $^{\Delta}$P <0.05

From Table 6.3 it can be seen that in ANAE positive cells, the various groups showed no clear difference, however AA murine CD_4 cells were clearly increased, and CD_8 cells were clearly reduced, thus CD_4/CD_8 was clearly elevated, and *Fengshiping* therapy is able to restore abnormal CD_4, CD_8, and CD_4/CD_8 antibodies to normal levels.

Experiment 7. Effect on murine abdominal cavity macrophage phagocytic function

50 NIH mice, weighing 18-22 g, half male and half female, were randomly divided into 5 groups, each perfused with the same volume at different doses of medication solution, once per day for one week.

1 h after the final dose of medication, the abdominal cavity of each mouse was infused with 0.2 mL 10% chicken red blood cells, after 4 h the mice were sacrificed, and abdominal cavity fluid obtained. The drip slide method was used to observe microscopically and determine the phagocytic CRBC macrophage count. The figures for macrophage phagocytic CRBC are shown in Table 7.

Table 7. Effect of *Fengshiping* on ICR murine abdominal cavity macrophage CRBC capacity

Group	Dose (g/kg)	Number of mice (per group)	Phagocytic percentage	Phagocytic index
Control	–	10	25.75 ±9.40	1.28 ±0.20
Fengshiping	27	10	33.20 ±12.77	1.46±0.36
Fengshiping	40.5	10	35.20 ±10.16	1.21 ±0.20
Fengshiping	60.9	10	37.78 ±20.14	1.53 ±0.32
Dexamethasone	0.005	10	8.33 ±10.13*	1.10 ±0.18

*P<0.05

From Table 7 it can be seen that at doses 27, 40.5 and 60.9 g/kg, *Fengshiping* had no clear effect on murine abdominal cavity macrophage phagocytic function.

Experiment 8. Effect on murine abdominal cavity capillary vessel hyperpermeability.

90 NIH mice, weighing 18-22 g, half male and half female, were randomly divided into 9 groups, respectively, and perfusion was performed with the same volume at differing doses of medication solution one time or once per day for 3 days. 1 h after the final medication dose, 0.7% HAC physiological saline solution was injected into the abdominal cavity of each mouse, and at the same time an iv of 0.1 mL/10 g 0.5% Evans blue physiological saline solution was administered. After 30 min the mice were sacrificed cervical vertebrae disjoint, the abdominal cavity was cut open, 5 mL physiological saline was used incrementally to rinse the abdominal cavity of each mouse, the rinsing solution was aspirated out, combined, and physiological saline was added at a constant volume to 8 mL/mouse. After centrifuging at 3000 rpm, the supernatant was used at a wavelength of 590 nm to detect the OD value. The results are shown in Table 8.

Table 8. Effect of *Fengshiping* on acetic acid-induced murine abdominal cavity capillary vessel hyperpermeability

Group	Dose (g/kg)	Medication administration frequency	Number of mice (per group)	Dye permeability	P value
Control	–	–	10	0.29 ±0.13	
Fengshiping	27	qd*1	10	0.26 ±0.14	>0.05
Fengshiping	40	qd*1	10	0.25 ±0.10	>0.05
Fengshiping	60	qd*1	10	0.25 ±0.09	>0.05
Control	–	–	10	0.28 ±0.15	
Fengshiping	27	qd*3	10	0.25 ±0.12	>0.05
Fengshiping	40	qd*3	10	0.18 ±0.10	>0.05
Fengshiping	60	qd*3	10	0.15 ±0.13	>0.05
Dexamethasone	0.15	qd*3	10	0.11 ±0.07	>0.01

From Table 8, the effect of *Fengshiping* on acetic acid-induced murine abdominal cavity capillary vessel hyperpermeability can be seen. When medication was administered once there was no clear effect, but when medication was administered three days in succession there were clear inhibition results.

Experiment 9. Effect of carrageenan-induced murine pleuritis exudation and inflammatory cell aggregation

After the mice were randomly divided into groups, at the tail vein each mouse was infused at 0.1 mL/10g body weight with 0.5% Evans blue physiological saline solution. The mice were lightly anesthetized with ether and at 0.03 mL/animal the right thoracic cavity was infused using a specially prepared syringe with a 1% carrageenan solution. At 4 h and 32 h after inflammation was induced, the mice were sacrificed, the abdomen was cut open to expose the diaphragmatic muscle, 1 mL injection device was used twice to infuse a total of 2 mL thoracic cavity washing solution, and the washing solution was collected in a test tube. 20 μL of the above-described washed out solution was added to 400 μL of white blood cell dilution solution, and a white blood cell blood count was performed under a microscope. The remaining solution was centrifuged at 3000 rpm for 10 min, supernatant was taken and at a wavelength of 600 nm site the optical density was detected. The thoracic cavity washing solution was used to correct the original solution to zero. The results can be seen in Table 9.

Table 9. Effect of *Fengshiping* on deerhorn vegetable capsule-induced murine pleuritis cell aggregation

Group	Dose (g/kg)	White blood cell count (2×10^5)		Dye exudation (OD)	
		4 h	32 h	4 h	32 h
Control	–	46.0 ±6.9	16.0 ±9.6	0.156 ±0.066	0.109 ±0.019
Fengshiping	27	26.8 ±4.5*	14.2 ±8.0	0.121 ±0.062	0.116 ±0.031
Fengshiping	40.5	10.9 ±4.0**	17.3 ±4.6	0.100 ±0.048	0.153 ±0.032
Fengshiping	60	8.0 ±5.5***	6.6 ±4.7*	0.129 ±0.066	0.092 ±0.051
Control	0.05	12.7 ±10.2**	4.4 ±4.0*	0.085 ±0.045	0.063 ±0.017

From Table 9 it can be seen that *Fengshiping* had clear inhibition results against murine pleuritis white blood cell aggregation. This effect was especially strong at early-stage aggregation; at 4 h the regression equation $y = 44.13\text{-}2.01x$, $r = -0.9625$ was obtained, weak against late-stage aggregation, and at 20 g/kg dose there were clear results and the effect on pleuritis exudation was not clear.

Experiment 10. Effect on rat CMC sac autologous cell aggregation.

64 SD rats weighing 150-180 g, half male and half female, were randomly divided into 8 groups, respectively, perfused with identical volume different doses of medication solution, one time or once per day for three days. One day prior to the day of the experiment, a 20 mL air sac was created at the back of the rat, into which was injected 20 mL of a 1% CMC solution. At 3.5 h and 7.5 h, 0.1 mL was aspirated out of each animal, placed in 0.01% brilliant cresyl blue PBS solution for staining, and under a microscope the CMC sac fluid white blood cell count was taken. The results are shown in Table 10.

Table 10. Effect of *Fengshiping* on rat carboxymethylcellulose sac white blood cell count

Group	Dose (g/kg)	Rat count (per group)	WBC count ($\times 10^7$/L) 3.5 h	7.5 h
Control	–	8	9.7 ±1.2	57.7 ±17.3
Fengshiping	27 ×1	8	8.5 ±3.5	39.4 ±16.5
Fengshiping	40 ×1	8	8.7 ±7.3	35.3 ±23.2
Fengshiping	60 ×1	8	6.6 ±3.3	18.1 ±8.6**
Control	-	8	10.97 ±6.7	35.6 ±11.2
Fengshiping	27×3	8	15.4 ±9.7	38.6 ±15.5
Fengshiping	40×3	8	4.8 ±3.4**	18.4 ±12.2**
Fengshiping	60×3	8	3.0 ±2.8**	11.0 ±9.2*
Prednisone	0.1×3	8	14.2 ±8.0	41.7 ±16.0
Control	–	8	10.9 ±3.0	41.3 ±6.9
Fengshiping	18 ×7	8	6.2 ±3.0*	11.4 ±6.4*
Fengshiping	27 ×7	8	3.7 ±1.7**	6.4 ±3.1**
Fengshiping	40 ×7	8	2.5 ±1.9**	5.9 ±3.9**
Prednisone	2mg ×1	8	1.5 ±0.7**	3.0 ±1.0**

Compared to the control **P <0.01

From Table 10 it can be seen that *Fengshiping* had a clear inhibitory effect on white blood cell aggregation in rat CMC sac and showed a clear dose – efficacy relationship. As medication administration time was extended the effect intensified; medication was administered for 7 days, at and 18 g/kg, e.g., it had an extremely clear inhibitory effect on white blood cell migration and prednisone intracapsular injection also had strong inhibition results.

Experiment 11. Effect on croton oil-induced murine ear inflammation

60 NIH mice, weighing 18-22 g, half male half female, were randomly divided into 6 groups, each perfused with the same volume in different doses of medication solution or *Astragalus* solution, once per day for three days. 1 h after the final medication administration, the left ear of each mouse was uniformly smeared on both sides of the auricle with 0.02 mL of 2% croton oil compound. After 4 h each mouse was sacrificed by cervical vertebrae disjoint, the left and the right ears cut out and the inflamed ear and the control ear weighed. The difference in weight in mg between the right and left ear was used to express the degree of ear inflammation. the results can be seen in Table 11.

Table 11. Effect of *Fengshiping* on croton oil-induced murine ear inflammation

Group	Dose (g/kg)	Number of mice (per group)	Degree of ear inflammation (mg)	Inhibition rate	P value
Control	–	10	44.38 ±9.40		
Fengshiping	27	10	39.05 ±12.33	12.00	>0.05
Fengshiping	40	10	36.65 ±5.83	17.64	<0.05
Fengshiping	60	10	34.91 ±9.71	21.34	<0.05
Dexamethasone	0.003	10	14.13 ±5.75	68.16	<0.01

From Table 11 it can be seen that *Fengshiping* had a clear inhibitory effect on croton oil-induced ear inflammation in mice, and it had a dose-efficacy relationship. however, the dose-efficacy relationship curve was fairly level, and at 13.5 g/kg there were clear inhibition results.

Experiment 12. Effect on acetic acid-induced body-twisting reaction in mice.

60 Kunming mice, weighing 18-22 g, half male half female, were randomly divided into 6 groups, each perfused with different doses of medication solution or *Astragalus* solution. 1 h after medication administration, 0.2 mL 0.7% HAC physiological saline solution was injected into the abdominal cavity. The mice were placed in fiberglass to observe the various latent stage body-twisting reactions for each mouse and body-twisting frequency in a 20-min period. The results are shown in Table 12.

Table 12. Effect of *Fengshiping* on acetic acid-induced murine body-twisting frequency

Group	Dose (g/kg)	Number of mice (per group)	Body-twisting frequency	Latent period (min)
Control	–	10	34.6 ±14.1	3.13 ±0.80
Fengshiping	27	10	28.2 ±5.76	3.82±0.85
Fengshiping	40	10	31.0 ±18.4	3.86 ±2.00
Fengshiping	60	10	20.7 ±12.3*	3.95 ±1.42
Tripterygium hypoglaucum (Level) Hutch	20	10	25.1 ±11.9	3.60 ±0.93
Morphine hydrochloride	10mg/kg	10	0.0 ±0.0	0.00 ±0.00

From Table 12 it can be seen that at a greater dose, *Fengshiping* was able to delay the onset of acetic acid-induced body-twisting reaction in mice and to clearly reduce the body-twisting frequency in a 20-min period, showing that *Fengshiping* had a definite analgesic effect.

Experiment 13. Effect on AA rat blood rheology.

SD rats weighing 180 ±20 g were each intradermally injected at the right rear foot metatarsal with 0.05 mL Freund's complete adjuvant to prepare an adjuvant arthritis model. In the negative control group, each right rear foot metatarsal was intradermally injected with 0.05 mL physiological saline. Three weeks

later the model was ready. The rats were divided into the model group, the high, middle and low dose groups, the negative control group and the positive control group. The positive control group was given *Tripterygium wilfordii* polyglucoside tablets. Medication was administered by perfusion once per day for 5 days. 1 h after the final medication administration, 3 mL of blood was taken from the abdominal aorta, and placed in a 1% heparin anticoagulant test tube. A NXE-1 model cone-style viscometer was used at 230, 115, 46, 23, 11.5 and 5.75 S^{-1} shearing rates to detect whole-blood viscosity. Using the WTP-B II model it was possible to adjust the constant-pressure capillary vessel viscometer to determine the plasma viscosity. The hematocrit tube centrifuge method was used to detect hematocrit. and the hemagglutination index and the red cell rigidity index were obtained by calculating the above-described results. The results are shown in Table 13.

Table 13. Effect on adjuvant arthritis rat blood rheology

Group	Control group	Model group	*Fengshiping* (30g/kg)	*Fengshiping* (15g/kg)	*Fengshiping* (7.5g/kg)	*Tripterygium wilfordii* polyglucoside (6mg/kg)
Whole blood viscosity (mPa·s)						
$230S^{-1}$	4.43 ±0.09	4.92 ±0.15**	4.56 ±0.09##	4.49 ±0.11##	4.54 ±0.16##	4.66 ±0.28#
1158^{-1}	5.17 ±0.25	5.81 ±0.19	5.33 ±0.09##	5.32 ±0.10##	5.16 ±0.14##	5.60 ±0.48#
$46S^{-1}$	6.84 ±0.11	7.20 ±0.18**	6.56 ±0.13##	6.59 ±0.09##	6.67 ±0.14##	6.70 ±0.48
$23S^{-1}$	8.10 ±0.15	8.23 ±0.38	7.95 ±0.22	7.93 ±0.12	7.97 ±0.14	8.02 ±0.14
$11.5S^{-1}$	9.35 ±0.08	9.78 ±0.10**	9.40 ±0.08##	9.45 ±0.10##	9.30 ±0.133	9.31 ±0.12##
$6.5S^{-1}$	11.03 ±0.14	12.66 ±0.31**	11.21 ±0.21##	11.29 ±0.19##	11.60 ±0.40##	11.42 ±0.52#
Plasma viscosity (mPa·s)	1.158 ±0.032	1.248 ±0.040**	1.161 ±0.011##	1.154 ±0.023##	1.156 ±0.018##	1.158 ±0.029#
Hematocrit (%)	46.13 ±2.31	41.33 ±1.12**	45.10 ±2.39##	44.33 ±1.52##	45.71 ±1.04##	46.03 ±3.59#
Hemagglutination index	2.49 ±0.032	2.58 ±0.083*	2.46 ±0.066#	2.49 ±0.094#	2.44 ±0.048##	2.45 ±0.091#
Red cell rigidity index	6.155 ±0.536	7.127 ±0.557**	6.506 ±0.558	6.525 ±0.146	6.394 ±0.200#	6.621 ±0.883

Compared to the negative control group *P <0.05, **P <0.01. compared to the model group #P <0.05, ##P <0.01

From Table 13 it can be seen that with the AA rat blood rheology model clear changes appeared, whole blood and blood plasma viscosity increased, hematocrit fell, and the hemagglutination index and rigidity index rose. *Fengshiping* therapy was able to make the above-described clear improvements to blood rheology indexes.

The above experiments prove the pharmacological effect of *Fengshiping*. Its many important pharmacological effects all have a good dose-efficacy relationship, showing that clinically it was possible to use a modulating dose to achieve optimal therapeutic efficacy.

Studies of the clinical efficacy of *Fengshiping* have been conducted in China, Japan, and Australia. With the use of *Fengshiping* capsules alone, results have been observed showing that, in accordance with international diagnosis, treatment and therapeutic efficacy standards for related disease, *Fengshiping* is 94% [of the time] somewhat effective against RA, about 60% [of the time] clearly effective, and able to quickly improve morning stiffness, inflammation pain, other symptoms, and RA-related detection indexes, as shown in Tables 14-21.

Table 14. Comparison of treatment group and control group results

Group	Number of cases	Alleviated (clinically cured)	Clear effect	Some effect	No effect	Clear effect rate	Some effect rate
Treatment group	32	5	14	11	2	59.38	93.74
Control group	30	3	10	12	5	43.33	83.33

Table 15. Effect on IgG, IgA and IgM

Group	Number of cases	IgG		IgA		IgM	
		Before	After	Before	After	Before	After
Normal people	32	12.45 ±1.48		2.37 ±1.00		1.58 ±0.59	
Treatment group	32	16.92 ±3.49	14.17 ±1.39**	3.65 ±1.03	2.39 ±1.18**	1.89 ±0.88	1.48 ±1.01
Control group	30	17.03 ±4.12	15.14 ±2.21**	3.45 ±1.86	2.32 ±1.75**	2.03 ±0.95	1.76 ±1.28

Compared to the pre-treatment group **P <0.01

Table 16. Effect on C3 and C4

Group	Number of cases (per group)	C3		C4	
		Before	After	Before	After
Normal people	32	0.62 ±0.13		0.14 ±0.15	
Treatment group	32	1.88 ±0.72	1.25 ±0.66**	0.48 ±0.12	0.26 ±0.06*
Control group	30	2.13 ±0.64	1.56 ±0.62**	0.40 ±0.16	0.25 ±0.07**

Compared to the pre-treatment group *P <0.05, **P <0.01

Table 17. Effect on ESR and CRP

Group	Number of cases (per group)	ESR		CRP	
		Before	After	Before	After
Normal people	32	8.37 ±5.26		4.12 ±1.88	
Treatment group	32	66.58 ±30.31	30.31 ±6.53**	13.35 ±6.67	8.86 ±3.34*
Control group	30	73.33 ±9.00	35.83 ±11.61**	14.21 ±6.29	9.04 ±3.15**

Compared to the pre-treatment group *P <0.05, **P <0.01

Table 18. Comparison of grip strength before and after treatment

Group	Treatment group		Control group	
	Before	After	Before	After
Grip strength left (mmHg)	39.13 ± 20.24(15)	80.47 ± 34.61**(15)	24.00 ± 17.63(21)	55.15 ± 23.27**(21)
Right	35.85 ± 22.46(15)	85.32 ± 36.32**(15)	22.80 ± 12.32(21)	58.17 ± 20.59**(21)

Compared to the pre-treatment group *P <0.05, **P <0.01

Table 19. Effect on joint inflammation and pain and morning stiffness

Item	Treatment group		Control group	
	Before	After	Before	After
Joint inflammation and pain	5.79 ±0.52	3.14 ±0.83*	5.56 ±2.15	2.92 ±0.26*
Morning stiffness time (min)	50.33 ±6.47	20.24 ±8.27**	48.75 ±8.34	27.50 ±3.78**

Compared to the pre-treatment group *P <0.05, **P <0.01

Table 20. Effect on RF negative conversion

Group	Number of cases	RF negative		
		Before treatment	After treatment	Negative conversion rate
Treatment group	32	24	11	54.2
Control group	30	18	10	44.4

At the same time that it is able to achieve clear therapeutic efficacy, *Fengshiping* is also able to reduce the patient's serum SIL-2R, STNF, SIL-6R and other indexes, as shown in Table 21.

Table 21. Effect on SIL-2R, STNF, SIL-6R and other primary indexes

Group	Number of cases	SIL-2R(u/mL)		STNF R1 (ng/mL)		SIL-6R (ng/mL)	
		Before	After	Before	After	Before	After
Normal people	32	299 ±68		1.56 ±0.48		72.05 ±18.26	
Fengshiping	15	(n = 32)		2.87 ±0.66	1.75 ±0.54**	(n = 22)	
Control group	10	683 ±189	381 ±157**	2.63 ±0.72	2.38 ±0.39	136.18 ±28.57	90.15 ±20.12**
		765 ±203	412 ±167**	(n = 8)		148.21 ±30.31	99.02 ±26.70**

Compared to pre-treatment ** P <0.01

Experience proves that the embodiments described below are able to achieve the above-described invention results.

Embodiment 1:

2222 g *Epimedium brevicornum Maximowicz*

2222 g *Tripterygium hypoglaucum (Level) Hutch*

1111 g *Cuscuta chinensis Lamarck*

1111 g *Lycium barbarum L.*

Using the four ingredients above, *Tripterygium hypoglaucum (Level) Hutch* is cut into pieces and 13x, 10x and 10x water is added, followed by three extractions. 1 h each time, *Epimedium brevicornum Maximowicz* is cut into sections, 15x, 10x and 10x the amount of water is added and three extractions are carried out 1 h each time. *Lycium barbarum L.* is pulverized to form a crude material, immersed in 20x water at 80°C for 1 h. *Cuscuta chinensis Lamarck* is pulverized into a crude powder and immersed in 31x water at 80°C for 1 h. The water decoctions or the water immersion fluids of the four materials are filtered separately, and separately passed through a large-pore adsorption resin column, then 70% ethanol is used for elution. When the runoff liquid is clearly darker in color, collection of the eluent is started. When the eluent color becomes extremely light, the elution is complete. Ethanol is recovered from each material eluent, concentrated, dried, thus obtaining the final extracted material powder. To each of the four extracted material powders is added medication-use starch to 200 g, mixed thoroughly, and packaged into 1000 capsules. The methods of the present invention are used to prepare a capsule with 0.2 g material inside it, and each capsule contains no less than 2.0 mg *Epimedium brevicornum Maximowicz* $C_{33}H_{40}O_{15}$. Routine indications are: oral, 3 times per day, 3 capsules each time.

Embodiment 2:

2000 g *Tripterygium hypoglaucum (Level) Hutch*

2000 g *Epimedium brevicornum Maximowicz*

Using the two ingredients above, *Tripterygium hypoglaucum (Level) Hutch* is cut into pieces and 13x, 10x and 10x is water added, followed by three extractions, 1 h each time. *Epimedium brevicornum Maximowicz* is cut into sections and 15x, 10x and 10x is water added, followed by three extractions, 1 h each time. The water decoctions of the materials are filtered and passed through a large-pore adsorption resin column, then 70% ethanol is used for elution. When the color of the runoff liquid is clearly darker, collection of the eluent is started. When the eluent color becomes extremely light the elution is complete. Ethanol is recovered from each material eluent, concentrated and dried, thus obtaining the extracted material powder. The extracted material powder is added to medication-use starch, mixed thoroughly, and packaged into 1000 capsules. The methods of the present invention are used to prepare a capsule packaged with 0.2 g of materials in each capsule, and each capsule contains no less than 2.0 mg *Epimedium brevicornum Maximowicz* $C_{33}H_{40}O_{15}$. Routine indications are: oral, 3 times per day, 3 capsules each time.

Embodiment 3:

2000 g *Tripterygium hypoglaucum (Level) Hutch*

2000 g *Epimedium brevicornum Maximowicz*

1000 g *Lycium barbarum L.*

Tripterygium hypoglaucum (Level) Hutch is cut into pieces and 13x, 10x and 10x water is added followed by three extractions, 1 h each time. *Epimedium brevicornum Maximowicz* is cut into sections, 15x, 10x and 10x waster is added, followed by three extractions, 1 h each time. *Lycium barbarum L.* is pulverized to form a crude material and immersed in 20x water at 80°C for 1 h. The water decoctions or the water immersion fluids of the materials are each filtered and passed through a large-pore adsorption resin column, then 70% ethanol is used for elution. When the color of the runoff liquid is clearly darker, collection of the eluent is started. When the eluent color becomes extremely light the elution is complete. Ethanol is recovered from each material eluent, concentrated and dried, thus obtaining an extracted material powder. The extracted material powders are added to medication-use starch, mixed thoroughly, and packaged into 1000 capsules. The methods of the present invention are used to prepare a capsule which is packaged with 0.2 g materials, and each capsule contains no less than 2.0 mg of *Epimedium brevicornum Maximowicz* $C_{33}H_{40}O_{15}$. The routine indications are: orally, 3 times per day, 3 capsules each time.

Embodiment 4:

2000 g *Tripterygium hypoglaucum (Level) Hutch*

2000 g *Epimedium brevicornum Maximowicz*

1000 g *Cuscuta chinensis Lamarck*

Tripterygium hypoglaucum (Level) Hutch is cut into pieces and 13x, 10x and 10x waster is added, followed by three extractions, 1 h each time. *Epimedium brevicornum Maximowicz* is cut into sections, 15x, 10x and 10x waster is added, followed by three extractions, 1 h each time. *Cuscuta chinensis Lamarck* is pulverized into a crude powder and immersed in 31x water at 80°C for 1 h. The water decoctions or water immersion fluids of the materials each filtered and passed through a large-pore adsorption resin column, then 70% ethanol is used for elution. When the color of the runoff liquid is clearly darker, collection of the eluent is started. When the eluent color becomes extremely light the elution is complete. Ethanol is recovered from each material eluent, concentrated and dried, thus obtaining the extracted material powder. The extracted material powders are added to medication-use starch, mixed thoroughly, and packaged into 1000 capsules. The methods of the present invention are used to prepare a capsule packaged with 0.2 g materials inside, and each capsule contains no less than 2.0 mg of *Epimedium brevicornum Maximowicz* $C_{33}H_{40}O_{15}$. Routine indications are: orally, 3 times per day, 3 capsules each time.

Embodiment 5:

2000 g *Tripterygium hypoglaucum (Level) Hutch*

1000 g *Cuscuta chinensis Lamarck*

Tripterygium hypoglaucum (Level) Hutch is cut into slices and 13x, 10x and 10x waster is added, followed by three extractions, 1 h each time. *Cuscuta chinensis Lamarck* is pulverized into a crude powder and immersed in 31x water at 80°C for 1 h. The water decoctions or water immersion fluids of the materials filtered and passed through a large-pore adsorption resin column, then 70% ethanol is used for elution. When the color of the runoff liquid is clearly darker, collection of the eluent is started. When the eluent color becomes extremely light the elution is complete. Ethanol is recovered from each material eluent, concentrated and dried, thus obtaining the extracted material powder. The extracted material is added to medication-use starch, mixed thoroughly, and packaged into 1000 capsules. The methods of the present invention are used to prepare a capsule with a daily dose equal to 30 g/day.

Embodiment 6:

2000 g *Tripterygium hypoglaucum (Level) Hutch*

1000 g *Lycium barbarum L.*

Tripterygium hypoglaucum (Level) Hutch is cut into pieces and 13x, 10x and 10x waster is added, followed by three extractions, 1 h each time. *Lycium barbarum L.* is pulverized into a crude material and immersed in 20x water at 80°C for 1 h. The water decoctions or water immersion fluids of the materials each filtered and passed through a large-pore adsorption resin column, then 70% ethanol is used for elution. When the color of the runoff liquid is clearly darker, collection of the eluent is started. When the eluent color becomes extremely light the elution is complete. Ethanol is recovered from each material

eluent, concentrated, and dried, thus obtaining the extracted material powder. The extracted material powder is added to medication-use starch, mixed thoroughly, and packaged into 1000 capsules. The methods of the present invention are used to prepare a capsule with a daily dose equivalent to 30 g/day.

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July 29, 2009

Re: 389-122045

To Whom It May Concern:

This is to certify that a professional translator on our staff who is skilled in the Chinese language translated "WO03086425A1 specification" from Chinese into English.

We certify that the English translation conforms essentially to the original Chinese language.

K Vitray

Kim Vitray
Operations Manager

Subscribed and sworn to before me this 29th day of June, 2009.

VICKI L. WUNNEBURGER
Notary Public, State of Texas
My Commission Expires
March 09, 2011

Vicki L Wunneburger

Vicki Wunneburger
Notary Public

910 WEST AVENUE, AUSTIN, TEXAS 78701 USA, +1 512-472-6753, 800-531-9977, FAX +1 512-472-4591

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PETITION FOR EXTENSION OF TIME
FROM THE OFFICE ACTION

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 29, 2009.

Alma R. Smalling

Applicant : Wenlong Deng
Confirmation No. 1639
Application No. : 10/510,617
Filed : October 7, 2004
Title : A PHARMACEUTICAL COMPOSITION FOR TREATING RHEUMATISM AND THE PREPARATION THEREOF

Grp./Div. : 1655
Examiner : Patricia A. Leith

Docket No. : 53624/C306

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Post Office Box 7068
Pasadena, CA 91109-7068
July 29, 2009

Commissioner:

Applicant petitions the Commissioner to extend the time for response to the Office action dated April 29, 2009 for one month(s) from June 29, 2009 to July 29, 2009.

The fee for extension of time required by 37 CFR § 1.17 is calculated below.

FEE CALCULATION			
LENGTH OF EXTENSION	SMALL ENTITY	LARGE ENTITY	FEE
WITHIN FIRST MONTH	$ 65.00	$ 130.00	$130.00
WITHIN SECOND MONTH	$ 245.00	$ 490.00	$
WITHIN THIRD MONTH	$ 555.00	$1,110.00	$
WITHIN FOURTH MONTH	$ 865.00	$1,730.00	$
WITHIN FIFTH MONTH	$1,175.00	$2,350.00	$

Submitted herewith is a check for $130.00 to cover the cost of the extension.

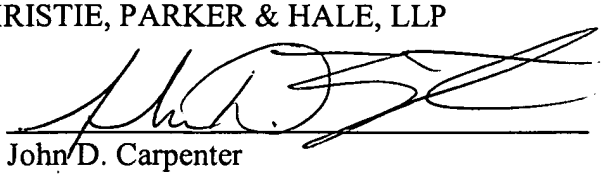
08/05/2009 LLANDGRA 00000013 031728 10510617
02 FC:1251 130.00 DA

Petition for Extension of Time
Application No. 10/510,617

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account. **A copy of this letter is enclosed.**

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By 

John D. Carpenter
Reg. No. 34,133
626/795-9900

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Atty. Docket No. 52994/328983

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
INTERNATIONAL SEARCHING AUTHORITY

Applicant:	ZAGHLOUL, Yasser A.
International Appln. No.:	PCT/US2007/011892
Filed:	18 May 2007 (18.05.2007)
Title:	OPTICAL LOGIC DEVICES HAVING POLARIZATION-BASED LOGIC LEVEL REPRESENTATION AND METHOD OF DESIGNING THE SAME

02 August 2009

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Alexandria, Virginia 22313-1450

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Attention: PCT Legal
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PO Box 1450
Alexandria, VA 22313-1450

ATTN: Arnessa Smith
Jon Kurtz
PCT Legal

RESPONSE TO NOTIFICATION DATED JULY 14 AND NOTIFICATION DATED JULY 28, 2009 AND PETITION UNDER 35 CFR 1.10

This response and petition is submitted in response to the Notification dated July 28, 2009. The IPEA improperly stated that the demand was made after the expiration of the time limit applicable under Rule 54bis.1(a). However, Applicant timely submitted the demand. The International Search Report was mailed on April 3, 2009; thus, pursuant to Rule 54bis. 1(a)(i), the demand was due on July 3, 2009, which is a federal holiday. Thus, pursuant to Rule 80.5, the due date was extended until July 6, 2009. The IPEA issued a Notification dated July 14 indicating that the payment for prescribes fees should be resubmitted to correct the "pay to" field, thereby suggesting that that the Demand had been considered timely submitted. However, Applicant subsequently received the Notification dated July 18 alleging that the demand was untimely. Thus, there appears to be two conflicting pronouncements from the IPEA.

Applicant filed a Demand via Express Mail pursuant to CFR 1.10 on July 6, 2009. As listed on the Demand under Box No. VI CHECK LIST, Applicant indicated that a Response to Written Opinion was also included as part of the Demand. Applicant placed the number of the Express Mail mailing label on the last page of the Response to Written Opinion, which constituted the last page of the Demand. Applicant has included (1) a true copy of the Express Mail mailing label showing the "date-in" as July 6, 2009; (2) a true copy of the receipt for the Express Mail mailing; and (3) the last page of the Demand having the number of the Express Mail mailing label.

In view of the forgoing, Applicant respectfully requests that the IPEA and the Director accord the demand a filing of July 6, 2009, and withdraw the Notification that the Demand was made after the expiration date.

Pursuant to the Notification dated July 14, 2009, Applicant encloses (with the response mailed to Jon Kurtz) a cashier's check in the amount of $771 and payable to "Director of the U.S. Patent and Trademark Office." If the IPEA and/or the Director continue to deem the demand untimely, Applicant respectfully requests the prompt refund of $771.00

Respectfully submitted,

Charlena L. Thorpe
Registration No. 48,035

THE LAW OFFICE OF CHARLENA THORPE, INC.
The Sugarloaf Center
2180 Satellite Boulevard Suite 400
Duluth, GA 30097
678-644-9922

"Express Mail" Mailing Label Number EH068161831
Date of Deposit: ~~06 July 2009~~ 03 August 2009 clt

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Charlena Thorpe

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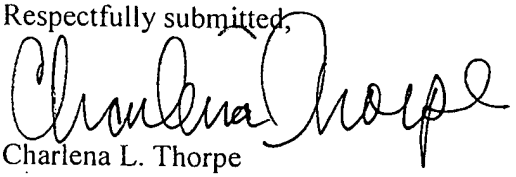
With respect to claims 35 and 49, the IPEA admitted that Lasher "does not specifically disclose a first control input." Yet, the IPEA states that, with respect to claim 45, "Lasher discloses a second control input. Through this inconsistency, and the lack of any explanation for how Lasher discloses the elements in claims 45 and 46, the IPEA has failed to clearly describe the reasons supporting the conclusion that claims 45 and 46 lack an inventive step as required under the PCT rules and regulations.

Conclusion

For the above reasons, claims 1-63 are novel in view of the art of record.

Respectfully submitted,



Charlena L. Thorpe
Registration No. 48,035

THE LAW OFFICE OF CHARLENA THORPE, INC.
The Sugarloaf Center
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678-644-9922

"Express Mail" Mailing Label Number EH710941427US
Date of Deposit: 06 July 2009

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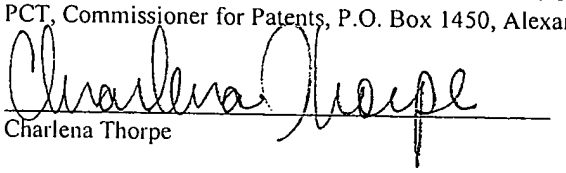

Charlena Thorpe